# iPS Cell-Based Treatment of Dominant Dystrophic Epidermolysis Bullosa

## Grant Award Details

iPS Cell-Based Treatment of Dominant Dystrophic Epidermolysis Bullosa

**Grant Type:** Disease Team Research I

**Grant Number:** DR1-01454

**Project Objective:** To develop a treatment for Dystrophic Epidermolysis Bullosa (DEB) using iPSC technology combined with gene therapy. The objective is to make autologous iPSC from DEB patients, correct the gene defect using homologous recombination and then differentiate the gene-corrected iPSC into skin grafts that can be returned to the patient.
The original goal of the project was to file an IND. CIRM and Grantee agreed that it would not be possible to achieve an IND filing within the award period, even with a 1-year NCE. The objective of the Wind-down NCE is to capture and publish the findings of the research conducted under this award.

**Investigator:**

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| **Name:** | Alfred Lane |
| **Institution:** | Stanford University |
| **Type:** | PI |

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| **Name:** | Anthony Oro |
| **Institution:** | Stanford University |
| **Type:** | Co-PI |

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| **Name:** | Marius Wernig |
| **Institution:** | Stanford University |
| **Type:** | Co-PI |

**Disease Focus:** Epidermolysis Bullosa, Pediatrics, Skin Disease

**Human Stem Cell Use:** iPS Cell

**Cell Line Generation:** iPS Cell

**Award Value:** $11,039,208

**Status:** Closed

## Progress Reports

**Reporting Period:** Year 1

**View Report**

**Reporting Period:** Year 2

**View Report**

**Reporting Period:** Year 3

**View Report**

**Reporting Period:** Year 4/5/NCE

**View Report**

## Grant Application Details

**Application Title:** iPS Cell-Based Treatment of Dominant Dystrophic Epidermolysis Bullosa

**Public Abstract:**

Genetic skin diseases constitute a diverse group of several hundred diseases that affect up to 2% of the population and include common disease such as psoriasis, atopic dermatitis, and wound healing. Patients with one genetic disease, dystrophic Epidermolysis bullosa (EB), lack a normal collagen VII (COL7A1) gene and suffer from debilitating blistering and scarring that can be lethal by young adulthood. The disease is devastating and despite all efforts, current therapy for DEB is limited to wound care. For recessive dystrophic EB (RDEB) where there is no COL7A1 protein, our EB Disease team has shown that retroviral delivery of the COL7A1 provides a powerful disease modifying activity as autologous, cell-based therapy. While successful, our initial approach cannot treat many dominantly inherited diseases such as dominant dystrophic EB (DDEB) where a poison subunit inhibits the function of the normal protein. Recent development of induced pluripotent stem (iPS) cells that are generated from the somatic cells of individual patients could provide an ideal source of therapy. Because of recent advances by our team and others in stem cell technology, our hypothesis is that we can create genetically-corrected iPS cells for dominant skin diseases such as DDEB. The goal of the EB Disease team is to complete the RDEB IND filing and then develop a next generation skin stem cell therapeutic for DDEB, based on defined genetic correction of the patient's mutation.

The project includes increasing the efficiency of iPS cell generation from patients cells, enhancing COL7A1 homologous recombination in iPS cells to correct the defect, and then improving the ability to return iPS cells back to skin keratinocytes. We will do extensive testing of the iPS-derived skin cells using human skin tissue models to ensure the safety and efficacy of these cells. Finally, we will work together with the FDA and the our collaborator Good Manufacturing Practice facility to generate patient-specific skin grafts for each patient in the clinical trial.

If successful, the approach in this project could be used to correct genetic defects in skin and other organs. The ability to therapeutically reprogram and replace diseased skin would allow this procedure to develop therapeutic reprogramming approaches for a variety of both common and life-threatening skin diseases. Moreover, genetically-corrected pluripotent iPS cells could form the basis of future systemic therapies to other organs besides the skin to treat common genetic disorders.

**Statement of Benefit to California:**

Genetic skin diseases constitute a diverse group of several hundred diseases that affect up to 2% of the population and include common disease that affect Californians such as psoriasis, atopic dermatitis, and wound healing. Patients with one genetic disease, dystrophic Epidermolysis bullosa (EB), lack collagen VII (COL7A1) and suffer from debilitating blistering and scarring that can be lethal by young adulthood. The disease is devastating and despite all efforts, current therapy for DEB is limited to palliative wound care.

For recessive dystrophic EB (RDEB), our EB Disease team has shown that retroviral delivery of the COL7A1 provides a powerful disease modifying activity as autologous, cell-based therapy. While successful, our initial approach is unable to treat many common, dominantly inherited diseases such as dominant dystrophic EB (DDEB). Recent development of induced pluripotent stem (iPS) cells that are generated from the somatic cells of individual patients could provide an ideal source of therapy. Our hypothesis is that we can develop genetically-corrected iPS cells for dominant skin diseases such as DDEB. The goal of the EB Disease team is to complete the RDEB IND filing and develop a next generation skin stem cell therapeutic for DDEB, based on defined genetic correction of the patient's mutation. The skin is an ideal tissue in which to initially try stem cell therapy because it is readily accessible, straightforward to observe, and any abnormal cells can be easily excised.

The project includes establishing a bank of DDEB cells from patients, and then increasing the efficiency of non-viral iPS cell generation, COL7A1 homologous recombination in iPS cells, and keratinocyte differentiation protocols. We will do extensive testing of the iPS-derived cells using human skin tissue models to ensure the safety of these cells. Finally, we will work together with the FDA and the our collaborator Good Manufacturing Practice facility to generate skin grafts for patients in the clinical trial.

If successful, the approach in this project could be used to correct many other genetic defects. The ability to therapeutically reprogram and replace skin would allow this procedure to develop therapeutic reprogramming approaches for a variety of both common and life-threatening skin diseases, bringing an enormous benefit to the people of California. Moreover, because a by-product of this project is corrected iPS cells that are pluripotent, patient-specific corrected iPS cells could form the basis of future systemic therapies to other organs besides the skin to treat common genetic disorders.

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